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Name.	Examiner Janet Higgins	Firm:	U.S. Patent Office
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FROM

Name:	Erich E. Veitenheimer, III, Ph.D.		
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Date Sent:	March 3, 2004	Number of Pages: *(including cover page)*	3

FAX MESSAGE

COMMENTS

Re: U.S. Patent Application No. 09/257,188 (Allowed)
Inventor: Gregory M. Glenn *et al.*
Title: *Use of Penetration Enhancers and Barrier Disruption Agents to Enhance the Transcutaneous Immune Response*
Our Reference: 056707-5001-US

As requested, please find attached page 17 of the specification and the sequence listing (1 page) for the above-identified application. If you need further assistance, please do not hesitate to contact me.

Heather C. Weber
Secretary to Erich E. Veitenheimer, III, Ph.D.
and Elizabeth C. Weimar

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Transcutaneous immunization with cholera toxin and related bAREs on the other hand is a novel immune response with an absence of superficial and microscopic post-immunization skin findings (i.e., non-inflamed skin) shown by the absence of lymphocyte infiltration 24, 48 and 120 hours after immunization. This is strikingly shown by completion of a Phase I trial in which humans were immunized with LT under a simple occlusive patch. Potent anti-LT IgG and IgA antibodies were stimulated. Two volunteers had biopsies performed at the site of immunization. Micro-scopic evaluation confirmed the clinical observation that no inflammation was seen. This suggests that Langerhans cells, which "comprise all of the accessory cell activity that is present in uninflammed epidermis, and in the current paradigm are essential for the initiation and propagation of immune responses directed against epicutaneously applied antigens" (Udey, 1997) may have been recruited. The uniqueness of the transcutaneous immune response here is also indicated by the both high levels of antigen-specific IgG antibody, and the type of antibody produced (e.g., IgG1, IgG2a, IgG2b, IgG3 and IgA) and the absence of anti-CT IgE antibody. However, other immune cells may be engaged and speculation on the mechanism should not limit the invention.

Thus, we have found that bacterial-derived toxins applied to the surface of the skin can activate Langerhans cells and that TCI induces a potent immune response manifested as high levels of antigen-specific circulating IgG antibodies and would expect that penetration enhancement would enhance the immune response. Transcutaneous adjuvant and penetration enhancer may be used in transcutaneous immunization to enhance the IgG antibody or T-cell response to proteins not otherwise immunogenic by themselves when placed on the skin.

Transcutaneous targeting of Langerhans cells may also be used to deactivate their antigen presenting function, thereby preventing immunization or sensitization. Techniques to mobilize Langerhans cells or other skin immune cells yet negatively modulate them include, for example, the use of anti-inflammatory steroidal or non-steroidal agents (NSAID), cyclophosphamide or other immunosuppressants, interleukin-10, TGFβ monoclonal antibody to interleukin-1, ICE inhibitors or depletion via superantigens such as through staphylococcal enterotoxin-A (SEA) induced epidermal Langerhans cell depletion.